REMARKS

Claim Amendments and New Claims

By the foregoing amendments, claims 1-3, 5-12, 14-57 and new claims 58-75 are pending in this application. Claims 4 and 13 have been canceled. Independent claims 1, 10, and 19 have been amended to recite a purified preparation (claim 1), or pharmaceutical composition or formulation (claims 10 and 19) comprising less than 2% of tissue factor pathway inhibitor (TFPI) or TFPI analog molecules that are carbamylated, as detected by cation exchange (CEX) chromatography. Dependent claims 3 and 12 have been amended to recite that less than about 1% of the TFPI or TFPI analog molecules are carbamylated. Support for these amendments is found in paragraph [59] and Table 1 on pages 15 and 18 of the specification, respectively.

Consistent with the above amendments, independent claims 20 and 31 have been amended to delete the phrase "wherein less than about 12% of the TFPI or TFPI analog molecules are modified...molecules." Claims 1, 10, 19, 20, 31, 39, and 50-57 have been amended to delete the reference to "large-scale" preparations and pharmaceutical compositions and formulations. Claims 8, 17, and 18 have been amended to improve clarity by deleting the phrases "members of" or "plurality of" the TFPI or TFPI analog molecules.

New independent claim 58 is directed to a method of preparing a pharmaceutical composition comprising TFPI or ala-TFPI molecules, less than 2% of which are carbamylated. The method comprises (a) purifying refolded TFPI or ala-TFPI that has been isolated from inclusion bodies, with a sequence of chromatography operations comprising two cation exchange chromatography operations, an anion exchange chromatography operation, and a hydrophobic interaction chromatography operation. Support is found in paragraph [64] on page 17 of the specification, describing a "sequence of chromatography operations"; paragraphs [87]-[95] on

pages 26-28 of the specification, describing TFPI isolation and refolding; and paragraphs [96]-[103] on pages 29-31 of the specification, describing each of the various chromatography operations. The method also comprises (b) concentrating and diafiltering purified, refolded preparation to provide a drug substance. Support is found in paragraphs [104]-[105] on page 31 of the specification. The method further comprises (c) formulating the drug substance into the pharmaceutical composition. Support is found in paragraph [106] on page 31 of the specification. New claims 59-68 depend from claim 58 and recite particular features of the purifying, concentrating, and formulating steps (a)-(c) as described in paragraphs [96]-[103] on pages 29-31 of the specification. New claim 69 recites a quantity of purified, refolded TFPI or ala-TFPI preparation, as recited in claim 50 and described in paragraph [30] on page 8 of the specification. New claim 70 depends from claim 58 and recites that the method further comprises, prior to step (a), (1) expressing the TFPI or ala-TFPI in an *E. coli* host cell, (2) isolating inclusion bodies containing the TFPI or ala-TFPI from the *E. coli* host cell, (3) isolating the TFPI or ala-TFPI from the inclusion bodies to obtain isolated TFPI or ala-TFPI, and (4) refolding the isolated TFPI or ala-TFPI to provide the refolded TFPI or ala-TFPI. Support is found in paragraphs [70]-[95] on pages 19-28 of the specification, describing these procedures in detail. New claims 71-75 depend from claim 70 and recite features of the *E. coli* host cell and plasmid. Support for these features is found particularly in paragraphs [72]-[76] on pages 20-22 of the specification.

The claim amendments and new claims add no new matter.

Compliance with Rejoinder Requirements of M.P.E.P. § 821.04

Claims 20-49 are withdrawn from consideration, as directed to non-elected subject matter in response to the November 1, 2005 requirement for restriction. Withdrawn method claims 20-

49 by virtue of their direct (claims 20, 31, and 39) or indirect (claims 21-30, 32-38, and 40-49) dependence on claim 1, incorporate the features of this elected composition claim. New claims 58-75 likewise recite the features of elected composition claim 1, as amended, namely that less than 2% of the TFPI or TFPI analog molecules are carbamylated. **The withdrawn claims and new claims are therefore of the same scope as elected, independent claim 1 and comply with the requirements under M.P.E.P. § 821.04 for rejoinder.** Applicants therefore respectfully request, upon a finding that the elected composition (preparation) claims 1-3, 5-9, and 50-55 are allowable, joinder of withdrawn method claims 20-49 and new claims 58-75.

Rejections over Diaz-Collier *et al.*, EPO publication EP 0 559 632 A1 ("Diaz-Collier")

Claims 1-19 and 50-57 have been rejected as either anticipated by, or obvious over, Diaz-Collier. The rejections of claims 4 and 13 have been rendered moot by the cancellation of these claims. Applicants respectfully traverse the rejections of claims 1-3, 5-12, 14-19, and 50-57 insofar as they apply to these claims as now amended.

The invention of the currently-rejected claims is associated with the discovery, after extensive research, of preparations and pharmaceutical formulations comprising TFPI or TFPI analogs which meet applicable FDA standards for purity in Phase III clinical trials. "The purification method of the invention produces preparations of TFPI or TFPI analog molecules that contain fewer modified TFPI or TFPI analog species than previous purification methods [known in the art]." See paragraph [63] on page 17 of the specification. See in particular the comparative data in Table 1 on page 18 of the specification, illustrating the improved purity of recombinant ala-TFPI obtained by "Process C" according to the invention. As demonstrated, the inventive method can provide a purity level of >99% as analyzed by cation exchange (CEX) HPLC, which is used to detect carbamylated molecules.

To advance prosecution, independent claims 1, 10, and 19 have been amended to recite a purified preparation (claim 1), or pharmaceutical composition or formulation (claims 10 and 19) comprising TFPI or TFPI analog molecules, less than 2% of which are carbamylated, as detected by cation exchange (CEX) chromatography. The remaining rejected claims are dependent on these amended claims. As acknowledged on page 6 of the Office Action, "The Examiner cannot make any speculations beyond the teachings of Diaz-Collier that the TFPI product of Example I is at least 95% homogeneous." Accordingly, from this disclosure of an at least 95% homogeneous TFPI product, there is no teaching or suggestion of a purified preparation, or pharmaceutical composition or formulation, comprising TFPI or TFPI analog molecules, *less than 2% of which* are carbamylated, as claimed. Nor is any teaching or suggestion of this recited purity level found in Chen *et al.*, U.S. Patent No. 6,525,102 ("Chen"), which is applied in combination with Diaz-Collier in the rejections under 35 U.S.C. § 103(a).

For a claim to be anticipated, every element and limitation of the claimed invention must be found in a single prior art reference. *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 58 USPQ2d 1286, 1291 (Fed. Cir. 2001). Also, it is black letter law that obviousness requires at least a suggestion of all of the features in a claim. See *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003). Diaz-Collier, whether taken alone or in combination with Chen, does not meet these legal standards for anticipation or obviousness, at least because these references fail to suggest a purified product comprising TFPI or TFPI analog molecules, less than 2% of which are carbamylated, as claimed.

Please withdraw the rejections under 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a).

CONCLUSION

In view of these remarks, all pending claims of this application are believed to be in condition for allowance. Acknowledgement of the same is respectfully requested, together with rejoinder of claims 20-49 and 58-75 in accordance with M.P.E.P. § 821.04. This response is believed to completely address all of the substantive issues raised in the Office Action dated October 7, 2008.

Please continue to direct all correspondence in this application to Novartis Vaccines and Diagnostics, Inc. (formerly Chiron Corporation), Intellectual Property Dept., R440, 4560 Horton Street, Emeryville, CA 94608-2916.

Respectfully submitted,

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